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EXAMINER	
HADDAD, MAHER M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,424	KARLIK ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8,10-13,15,16,18-20,22-46,48 and 52-56* is/are pending in the application.

4a) Of the above claim(s) *25-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-8, 10-13, 15-20, 22-24, 46, 48 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 6-8, 10-13, 15, 16, 18-20, 22-46, 48 and 52-56 are pending.

2. Claims 25-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

3. Claims 1, 6-8, 10-13, 15-20, 22-24, 46, 48 and 52-56 are under examination as they read on an examination as they read on a method of promoting remyelination of nerve cells or reversing paralysis in a mammal comprising administering a remyelinating agent.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 6-8, 10-13, 15-20, 22-24, 46, 48 and 52-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-7, 11-13, 28 and 29 of copending Application No. 11/540,640. Although the conflicting claims are not identical, they are not patentably distinct from each other because the `640 Application claims the same method of chronically reducing pathological inflammation in a patient in need thereof comprising chronically administering an agent to the patient that inhibits alpha-4 integrin or inhibits a dimer comprising alpha-4 integrin in a therapeutically effective amount; wherein the

chronic administration is for a period of at least 6 months, the pathological inflammation is caused by multiple sclerosis, the agent is natalizumab or an immunologically active fragment thereof, and the therapeutically effective amount is sufficient to relieve symptoms of multiple sclerosis (claim 1), wherein the chronic administration is for a period of at least 12 months (claim 3), wherein the agent is administered repeatedly in a manner to bind to alpha-4 integrin or a dimer comprising alpha-4 integrin, and wherein the administration maintains alpha-4 integrin receptor saturation at a level sufficient to chronically suppress pathological inflammation in the patient (claim 4), wherein the alpha-4 integrin dimer is alpha-4 beta-1 (claim 11), wherein the agent is administered in amount sufficient to saturate at least one alpha-4 integrin dimer receptor thereby inhibiting pathological inflammation, wherein the dimer receptors are alpha-4 beta-1 or alphas4 beta-7, and the pathological inflammation is caused by multiple sclerosis (claim 13), wherein natalizumab is administered by infusion every four weeks for at least 6 months in an amount of about 1 mg/kg patient to about 20 mg/kg patient (claim 28), wherein the infusions are administered for at least 12 months (claim 29). "promoting remyelination of nerve cells" is considered inherent to the method of chronically reducing pathological inflammation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e1) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

7. Claims 1, 6-8, 10-13, 15-20, 22-24, 46, 48 and 52-56 are rejected under 35 U.S.C. 102(a)/(e) as being anticipated by US 20070025989 (102(e)) or WO/2003/072040.

Since the teachings of the `989 publication is the same as the `040 publication. The teachings of the `989 publication is used to make the rejection.

The `898 publication teaches and claims methods of chronically reducing pathological inflammation in a patient in need thereof comprising chronically administering an agent to the

patient that inhibits alpha-4 integrin or inhibits a dimer comprising alpha-4 integrin in a therapeutically effective amount (see published claim 1), wherein the chronic administration is for a period of at least 6 months (see published claim 2) or a period of at least 12 months (see published claim 3), wherein the agent is administered repeatedly in a manner to bind to alpha-4 integrin, and wherein the administration maintains alpha-4 integrin receptor saturation at a level sufficient to chronically suppress pathological inflammation in the patient (see published claim 4), wherein the agent is a monoclonal antibody or an immunogically active fragment thereof (see published claim 9), wherein the fragment of the monoclonal antibody is an Fab, scFv or F(ab')2 (see ¶56), wherein the monoclonal antibody is natalizumab (a genetically engineered antibody, chimeric antibody that is a humanized antibody) (see published claim 10), which administered intravenously (see ¶151), wherein the alpha-4 integrin dimer is alpha-4 beta-1 (see published claim 11), wherein the agent is administered in amount sufficient to saturate at least one alpha-4 integrin dimer receptor thereby inhibiting pathological inflammation (see published claim 12), wherein the dimer receptors are alpha-4 beta-1 or alpha-4 beta-7, and the pathological inflammation is caused by multiple sclerosis (see published claims 13 and 18), wherein the chronic administration of such agent is in combination with other agents (see ¶51, 120, 124, 125) such as non-steroidal anti-inflammatory agents (NS such as ibuprofen, naproxen and ketoprofen), or a corticosteroide or glatirmaer (¶ 136) e.g., prednisone, methylprednisolone, dexamethasone and the like (¶137). The `898 publication teaches that in an animal model for multiple sclerosis, murine monoclonal antibodies directed against alpha-4 beta-1 integrin have been shown to block the adhesion of leukocytes to the endothelium, and thus prevent inflammation of the central nervous system and subsequent paralysis in the animals (¶113).

"promoting remyelination of nerve cells" is considered inherent to the method of chronically reducing pathological inflammation.

The reference teachings anticipate the claimed invention.

8. Claims 1, 6-8, 10-13, 15-16, 46, 48 and 52-56 stand rejected under 35 U.S.C. 102(a) as being anticipated by Miller et al (N Engl J Med. 2003 Jan 2;348(1):15-23).

In a randomized, double-blind trial, Miller et al teach randomly assigned a total of 213 patients with relapsing-remitting or relapsing secondary progressive multiple sclerosis to receive 3 mg of intravenous natalizumab per kilogram of body weight (68 patients), 6 mg per kilogram (74 patients), or placebo (71 patients) every 28 days for 6 months. Miller et al teach that in a placebo-controlled trial, treatment with natalizumab led to fewer inflammatory brain lesions and fewer relapses over a six-month period in patients with relapsing multiple sclerosis (see abstract). Further, the α_4 integrin–specific humanized monoclonal antibody natalizumab suppressed the formation of gadolinium-enhancing inflammatory brain lesions over the six-month treatment period. This effect was evident one month after the first infusion and was sustained throughout the treatment period. The reduction in the formation of lesions was approximately 90 percent at a dose of both 3 mg per kilogram and 6 mg per kilogram and was thus greater than the reduction of 50 to 80 percent reported with the β-interferons and the reduction of approximately 30 percent

reported with glatiramer acetate (see page 21, 1st col., 1st¶]). Ongoing longer-term studies of natalizumab will provide more definitive data (see page 22, 1st col., last sentence).

The reference teachings anticipate the claim invention.

9. Claims 1, 6-8, 10-13, 15-16, 18-20, 22-24, 46, 48 and 52-56 stand rejected under 35 U.S.C. 102(a) as being anticipated by National Horizon Scanning Centre article (July 2002).

The article teaches that patients with relapsing-remitting MS (multiple sclerosis) or secondary progressive MS received either IV natalizumab (humanized anti-VLA-4) (3mg/kg or 6mg/kg) or placebo every 4 weeks for 6 months. MRI results showed that patients treated with natalizumab for 6 months had fewer new brain lesions than those treated wit placebo. A reduction in the number of relapses was also observed, with 34 relapses in the control group compared with 19 in the low dose and 14 in the high dose natalizumab group (see page 3, under Effectiveness). The article teaches that seventy two patients with relapsing-remitting and secondary progressive MS took part in a ranomised double-blind, placebo controlled trial. Each patient received two iv infusions of 3mg/kg natalizumab or placebo four weeks apart and were followed up for 24 weeks with serial MRI and clinical assessment. Significantly fewer new brain lesions were observed in the treated group compared with the control group after first 12 weeks (see page 3, under Effectiveness).

The article teaches that four general methods of disease management target separately or in combination, different aspects of the disease including treatment of relapses with corticosteroids (see page 3, under Current treatment and alternatives).

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 6/17/09, have been fully considered, but have not been found convincing.

Applicant submits that the National Horizon indicates that the treated patients were still developing new brain lesions and still displayed relapses. Applicant concluded that the National Horizons treatment regimen may have slowed an aspect of disease progression, however, National Horizon does not teach a method that promoted remyelination or reversal of paralysis. Applicant further asserts that the National Horizon article does not teach Applicant's method for promoting remyelination of nerve cells by chronically administering an antibody that binds to alpha-4beta-1 integrin, e.g., natalizumab, in a remyelinating effective amount weekly or monthly over a period of at least 6 months, or at least one year as recited in claim 18 and 56.

This is not persuasive. It appears that applicant and the examiner differ on interpretation of both the claimed methods and the prior art. Also, applicant relies upon an asserted and claimed mechanism of action but does not provide objective evidence that the prior art teaching of treating the same MS patient populations with the same compositions, monthly for at least 6

months, to achieve the same therapeutic effect differs from the claimed methods. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which natalizumab treat MS does not appear to distinguish the prior art teaching the same methods to achieve the same end result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. *In re Baxter Travenol Labs*, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 6-8, 10-13, 15-16, 18, 46, 48 and 52-56 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tubridy et al (Neurology, 1999 Aug 11;53(3):466-72) for the same reasons of record.

Applicant submits that their teaching for chronic administration of natalizumab has displayed unexpected benefits in the treatment of demyelinating conditions, e.g., multiple sclerosis. Applicant points to Munschauer and Polman article to support Applicants disclosure that the chronic administration of natalizumab over time not only promote remyelination but it also reverses paralysis in subjects.

However, Polman studies yielded a treatment effect size after one year (a 68% reduction in relapse rate compared to placebo, a dramatic reduction in relapse rate, new or enlarging T2-hyperintense lesions, and mean number of gadolinium-enhancing lesions was observed) is a predictable results (rather than unexpected benefits) given the teachings of Tubridy that the treated group with anti-α4 integrin antibodies exhibited significantly fewer new active lesions and new enhancing lesions than the placebo group over the first 12 weeks. Tubridy et al explicitly suggest the use of a higher dose of Antegren (natalizumab) administered chronically will need to be evaluated in future studies (see page 471, 2nd col., 2nd full ¶). Tubridy et al

concluded that the treatment was well tolerated. And further studies will be required to determine the longer term effect of this treatment on MRI and clinical out comes (abstract). Those of skill in the art would have had reason to chronically administer the anti-α4 antibody of Tubridy to evaluate the effect of anti-α4 integrin antibody on brain lesion activity in MS.

Further showing of unexpected results must be commensurate in scope with the invention as claimed. The claims are drawn to promoting remyelination of nerve cells in a mammal comprising chronically administering an antibody or an immunologically active fragment thereof that binds to alpha-4beta1 integrin. Nothing in Munschauer et al or Polman shows promoting remyelination of nerve cells as Applicant claims. No reverses paralysis has been shown either. Munschauer et al and Polman et al teachings with respect to promoting remyelination and reverses paralysis with specific anti-alpha4 antibody does not commensurate in scope with the generic anti-alpha4beta-1 integrin antibodies. Clearly, Polman teach that relapsing multiple sclerosis is characterized by the intermittent development of inflammatory lesions in the brain and spinal cord, resulting in plaques of demyelination and axonal loss (see page 900, 1st col., 1st ¶). Accordingly, "promoting remyelination and reverse paralysis" is a consequence of chronically reduced pathological inflammation. Therefore, it is an inherent property to the chronically administration of the natalizumab to treat the chronic inflammation of multiple sclerosis suggested by Tubridy et al.

Applicant argues that promoting remyelination is to promote repair and/or regeneration of the myelin sheath of nerve cells. Promoting remyelinatio nis significantly different from stoping disease progression. Applicants submit that any method used to treat MS that treats and stops disease progression might treat and stop myelin degradation. However, stopping disease progression, including the loss of the myelin sheath, is distinct from promoting repair and/or regeneration of the myelin sheath. The knowledge that certain compounds are useful for treating and stopping myelin degradation would not lead one of ordinary skill in the art to understand that the compounds could be used to promote repair and/or regeneration of the myelin sheaths. Applicant points to Dubois-Daleq that "while therapies designed to reduce inflammation can decrease the disease burden, they do not directly address the question of myelin repair in chronic disease. Recent advances in the stem cell field, and in particular the biology of adult neural precursor cells, have raised hopes that remyelinating therapies may soon be developed."

However, Polman teaches that relapsing multiple sclerosis is characterized by the intermittent development of inflammatory lesions in the brain and spinal cord, resulting in plaques of demyelination and axonal loss (seep page 900, 1st col., top ¶). While those skilled in the art would always continue to search for therapies to promote remyelination, Applicant's arguments including the issue of long-felt need are not found persuasive of patentability when the claimed invention would flow logically from the teaching of the prior art of record.

Applicant submits that Tubridy administered anti-α4 integrin antibody in two IV infusions 4 weeks apart and then followed the patients for 24 weeks. Tubridy teaches that at 12 weeks the treated group exhibited significantly fewer new active lesions and fewer new enhancing lesions than the placebo group but by 24 weeks there were no significant difference in the number of

new active or new enhancing lesion between the groups. Applicant concluded that Tubridy teaches a regimen that may slow progression of the disease, but there is no teaching or suggestion of regiment that stops disease progression or would promote remyelination or reverse paralysis.

Contrary to Applicant's assertions, Tubridy et al explicitly suggest the use of a higher dose of Antegren (natalizumab) administered chronically will need to be evaluated in future studies (see page 471, 2nd col., 2nd full ¶).

Applicant argues that Tubridy states that their study was not designed to look definitively at the effect of treatment on relapse rate and that the correlation between disability and changes seen on MRI would require a larger longer term trial and that the use of higher doses and chronic administration would require further studies. Applicant submits that based on such a general suggestion for approaching further studies, and based on the knowledge that prior to Applicants' invention none of the available treatments promoted remyelination or reversed paralysis, One of skill in the art would not have had a reasonable expectation that an anti-α4 integrin antibody would promote remyelination and actually reverse paralysis. Applicant concluded that the remyeliantion and reversal of paralysis produced by Applicants' claimed method of chronically administering of a remyelinating amount of anti-α4 integrin antibodies, e.g., natalizumab, over a period of at least 6 month, or at least year is a surprising and unexpected result. As such Tubridy does nto render Applicants invention as claimed obvious.

However, Applicant fails to show that the anti-α4 integrin antibody on its own would promote remyelination or nerve cells and reverse paralysis. In the contrary, the specification under ¶2717 discloses that remyelinating antibodies, such as natalizumab, reverse disease pathology in EAE by inhibiting the otherwise continuous influx of new inflammatory cells. It would be conventional and within the skill of the art to easily adapt Tubridy et al chronic administration of anti-α4 antibodies to study the longer term and clinical outcome effect of the natalizumab on MS treatment, specially since the natalizumab treatment was well tolerated and show short-term treatment with natalizumab results in a significant reduction in the number of new active lesions on MRI. Further, the Tubridy et al teachings suggest using the chronic administration of natalizumab to study its effect on disability in MS patients.

12. Claims 1, 6-8, 10-13, 15-16, 18, 46, 48 and 52-56 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 5,840,299 in view of Tubridy et al (Neurology, 1999 Aug 11;53(3):466-72).

The `299 patent teaches a method of treating central nervous system in patient (human) comprising administering to the patient a composition comprising humanized MAB 21.6 (i.e., anti-alpha4beta1 antibody, natalizumab) to block α4-dependent interactions of the VLA-4 receptor (see col., 14, under Methods of Treatment and claims 27-29 in particular). Furthermore, the `299 patent teaches a binding fragment of the humanized antibody. The fragments exhibit specific binding to the VLA-4 antigen, wherein humanized antibody fragments include separate

heavy chains, light chains Fab, Fab', $F(ab')_2$, Fabc, and Fv (see col., 12, under Fragments of Humanized antibodies in particular). In addition, the `299 patent teaches that chimeric light and heavy chains were constructed for the mouse 21.6 $V_L$ and $V_H$ regions (see Example 2, col., 18in particular). The `299 patent also teaches the monoclonal antibody 21.6 (see col., 3, lines 36-39 in particular). The `299 patent teaches that the pharmaccutical compositions can be administered by intravenous or subcutaneous administration. (see col., 15, lines 59-65 in particular). Furthermore, the antibody is administered by intravenous infusion or subcutaneous injection at a dose from 1 to 5 mg antibody per kilo of bodyweight. The dose is repeated at interval from 2 to 8 weeks. Within this range, the preferred treatment regimen is 3 mg antibody per kilo of bodyweight repeated at a 4 week interval (see col., 16, lines 17-22 in particular).

The `299 patent teaches compositions are administered to a patient suspected of, or already suffering from a disease such as multiple sclerosis, in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a therapeutically- or pharmaceutically-effective dose (see col., 15, lines 41-50). The `299 patent teaches that effective doses of the compositions of the present invention, for the treatment of the above described conditions will vary depending upon many different factors, including means of administration, target site, physiological state of the patient, and other medicants administered (see col., 16, lines 6-18).

Claims 15 and 16 are included because the express dosage amount are material claim limitations however, the statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim.

While the `299 patent is silence with regard to "remyelination of nerve cells" and "reversing paralysis" per se; the method, the product used in the reference method are the same as the claimed method. Therefore these limitations are considered inherent properties.

The reference teachings does not explicitly teach the chronic administration of anti-VLA-4 is weekly or monthly over a period of at least six moths in claims 1 and 46 or at least one year in claims 18 and 56.

However, Tubridy et al teach that short-term treatment with monoclonal antibody against $\alpha 4$ integrin results in a significant reduction in the number of new active lesions on MRI in MS. Tubridy et al teach that the relatively modest correlation between disability and changes seen on MRI means that any potential new treatment must ultimately be tested in a larger, longer term trial. Finally, Tubridy et al teach that a higher dose of natalizumab administered chronically will need to be evaluated in future studies (see abstract and page 471, 2nd col., 1st and 2nd ¶).

Given that the MS is a chronic disease, and that the `299 patent teachings that administered to a patient suspected of, or already suffering from a disease such as multiple sclerosis, in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a therapeutically- or pharmaceutically-

effective dose (see col., 15, lines 41-50), it would be conventional and within the skill of the art to chronically administer the anti-VLA-4 as taught by Tubridy et al, weekly or monthly for at least six months/one year. The determination of the optimal intervals of treatment is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. The duration of treatment, the specific rout of administration and like factors within the knowledge and expertise of the medical practitioner. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

As to the administration of the anti-VLA-4 antibodies weekly or monthly over a period of at least six months, such dosing and modes of administration are result effective variables.

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

As dosing and modes of administration are known to the ordinary artisan, it would have been obvious to optimize both the dosing regimens and mode of administration to meet the needs of the patient at the time the invention was made.

Given the clear teachings of the prior art to treat MS with humanized MAB 21.6 antibodies to block α4-dependent interactions of the VLA-4 receptor including in therapeutic regimens for treating disease such as multiple sclerosis, in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease and its complications; one of ordinary skill in the art at the time the invention was made would have been motivated to administer various therapeutic regimens including the treatment of MS with anti-VLA-4 antibodies weekly or monthly over a period of at least six months, at the time the invention was made.

The various dosing regimens encompassed by the instant claims were obvious at the time the invention was made, given that it was well known and practice at the time the invention was made to provide immunotherapy based upon the condition and needs of the patient, as evidenced by the teachings of the prior art.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Applicant's arguments, filed 6/17/09, have been fully considered, but have not been found convincing.

Applicants submit that their teachings for chronic administration of natalizumab has displayed unexpectedly significant benefits in the treatment of multiple sclerosis, i.e., for the first time a treatment has produced remyelination and reversal of paralysis in MS patients. Additional reports have published that support Applicants' teachings that the chronic administration of natalizumab over time not only promotes remyelination but it also reverses paralysis in subjects. In addition to Munshauer and Polman submitted with Applicants' previous response, Applicants submit herewith Zivadinov et al. "Natalizumab (Tysabri) Promotes Remyelination in Patients with Multiple Sclerosis. A Voxel- Wise Magnetization Transfer Imaging Case-Control Study" presented April 28, 2009 at the American Academy of Neurology (AAN), which further demonstrates that chronic administration of natalizumab in remyelinating effective amounts resulted in remyelination and stabilizes demyelination.

However, the asserted unexpected results are considered inherent property of a method for treating multiple sclerosis by chronically administering natalizumab. The claims purport to be a method for "promoting remyelination of nerve cells" is an old therapy with the inherent results of the old therapy. With respect to applicant's arguments concerning the remyelination effect of the natalizumab according to the claimed method, although the reference teachings do not explicitly teach the same mechanism of nerve remyelination, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). Also, regarding process claims, a preamble recitation that merely expresses the purpose of performing the claimed steps

is not a limitation on the process where the body of the claim fully sets forth the steps required to practice the claimed process, and where the preamble recitation does not affect how the claimed steps are to be performed. *See Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375-76 (Fed. Cir. 2001).

Thus, in *Bristol-Myers*, the court held that preamble language stating that a treatment method was "for reducing hematologic toxicity" did not limit the claim since the steps would be "performed in the same way regardless whether or not the patient experiences a reduction in hematologic toxicity, and the language of the claim itself strongly suggests the independence of the preamble from the body of the claim." *Id.* at 1375. The *Bristol-Myers* court similarly held that preamble language reciting "[a] method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity" did not limit the treatment method claim because it was "only a statement of purpose and intended result. The expression does not result in a manipulative difference in the steps of the claim." *Id.* at 1375-76.

Applicant submits that the `299 patent and Tubridy in combination fail to suggest the unexpected benefits produced by Applicants' method as claimed.

It is the Examiner's position that it would be conventional and within the skill of the art to chronically administer the anti-VLA-4 as taught by Tubridy et al, weekly or monthly for at least six months/one year. It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

Applicant submits that the '299 Patent does not teach the chronic administration of the antibody over a period of at least 6 months or at least 1 year and is silent regarding "remyelination of nerve cells" and "reversing paralysis." Furthermore, Tubridy teaches that at 24 weeks after patients received two IV administration of anti-α4 integrin antibody 4 weeks apart there were no significant difference in the number of new active or new enhancing lesions between the groups of treated and control patients. Thus Tubridy teaches a regimen that may slow progression of the disease, but there is no teaching or suggestion of a regimen that would promote remyelination or reverse parlysis. Likewise, National Horizon, teaches that administration of natalizmab every four weeks for six months only slowed the occurrence of new brain lesions but does not teach the surprising and unexpected result that chronic treatment with an antibody such as natalizumab over a period of at least 6 months or at least a year actually promotes remyelination and reversal of paralysis. Thus one of skill in the art considering the '299 Patent in combination with Tubridy would not expect that the chronic administration of natalizumab over a period of at least 6 months, or at least a year for claims 18 and 56, would promote remyelination and reverse paralysis.

However, the `299 patent teaches that the animal experiments test the effect of anti-VLA-4 antibodies on animals having an artificially induced condition, simulating multiple sclerosis, wherein the experiments show that administration of anti-VLA-4 antibodies prevents inflammation of brain and *subsequent paralysis in the animals* (see col., 1 line 66 through col. 2, line 8 in particular). Tubridy et al explicitly suggest the use of a higher dose of Antegren (natalizumab) administered chronically will need to be evaluated in future studies (see page 471, 2nd col., 2nd full ¶). Given that the MS is a chronic disease, and that the `299 patent teachings that administered to a patient suspected of, or already suffering from a disease such as multiple sclerosis, in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a therapeutically- or pharmaceutically-effective dose (see col., 15, lines 41-50), it would be conventional and within the skill of the art to chronically administer the anti-VLA-4 as taught by Tubridy et al, weekly or monthly for at least six months/one year. The determination of the optimal intervals of treatment is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. The duration of treatment, the specific rout of administration and like factors within the knowledge and expertise of the medical practitioner. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

13. Claims 1, 19-20 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 5,840,299, each in view of Tubridy et al, and further in view of U.S. Pat. No 6,753,135.

The teachings of the `299 patent and Tubridy et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of that the corticosteroid is prednisone in claims 23.

The `135 patent teaches that prednisone is a corticosteroid used to treat a wide variety of inflammatory disorders, including multiple sclerosis. The `135 patent further teaches that the prednisone and other glucocorticoids are known to have broad-ranging anti-inflammatory and immunosuppressive effects, including inhibition of pro-inflammatory mediators and activation of anti-inflammatory mediators. They affect the growth, differentiation, and function of monocytes and lymphocytes; the distribution of cellular subsets; and the production of cytokines, cellular proteins that are secreted and affect the behavior of other cells. (see col., 1 lines 30-45 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to co-administer prednisone taught by the `135 patent with anti-VLA-4 antibodies taught by the ` `299 patent in view of Tubridy et al in a method of promoting remyelinating of nerve cell/reversing paralysis in MM subject.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because prednisone is used to treat a wide variety of inflammatory disorders, including multiple sclerosis as taught by the `135 patent. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 1, 19-20 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al, and further in view of U.S. Pat. No 6,753,135.

The teachings of Miller et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of that the corticosteroide is prednisone in claims 23.

The `135 patent teaches that prednisone is a corticosteroid used to treat a wide variety of inflammatory disorders, including multiple sclerosis. The `135 patent further teaches that the prednisone and other glucocorticoids are known to have broad-ranging anti-inflammatory and immunosuppressive effects, including inhibition of pro-inflammatory mediators and activation of anti-inflammatory mediators. They affect the growth, differentiation, and function of monocytes and lymphocytes; the distribution of cellular subsets; and the production of cytokines, cellular proteins that are secreted and affect the behavior of other cells. (see col., 1 lines 30-45 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to co-administer prednisone taught by the `135 patent with the anti-VLA-4 antibody, natalizumab taught by Miller et al in a method of promoting remyelinating of nerve cell/reversing paralysis in MM subject.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because prednisone is used to treat a wide variety of inflammatory disorders, including multiple sclerosis as taught by the `135 patent. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 8, 2009

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